Incidence of Cancer and Mortality Following α-Tocopherol and β-Carotene Supplementation

A Postintervention Follow-up

The ATBC Study Group

Context In the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, α-tocopherol supplementation decreased prostate cancer incidence, whereas β-carotene increased the risk of lung cancer and total mortality. Postintervention follow-up provides information regarding duration of the intervention effects and may reveal potential late effects of these antioxidants.

Objective To analyze postintervention effects of α-tocopherol and β-carotene on cancer incidence and total and cause-specific mortality.

Design, Setting, and Participants Postintervention follow-up assessment of cancer incidence and cause-specific mortality (6 years [May 1, 1993-April 30, 1999]) and total mortality (8 years [May 1, 1993-April 30, 2001]) of 25563 men. In the ATBC Study, 29133 male smokers aged 50 to 69 years received α-tocopherol (50 mg), β-carotene (20 mg), both agents, or placebo daily for 5 to 8 years. End point information was obtained from the Finnish Cancer Registry and the Register of Causes of Death. Cancer cases were confirmed through medical record review.

Main Outcome Measures Site-specific cancer incidence and total and cause-specific mortality and calendar time-specific risk for lung cancer incidence and total mortality.

Results Overall posttrial relative risk (RR) for lung cancer incidence (n=1037) was 1.06 (95% confidence interval [CI], 0.94-1.20) among recipients of β-carotene compared with nonrecipients. For prostate cancer incidence (n=672), the RR was 0.88 (95% CI, 0.76-1.03) for participants receiving α-tocopherol compared with nonrecipients. No late preventive effects on other cancers were observed for either supplement. There were 7261 individuals who died by April 30, 2001, during the posttrial follow-up period; the RR was 1.01 (95% CI, 0.96-1.05) for α-tocopherol recipients vs nonrecipients and 1.07 (95% CI, 1.02-1.12) for β-carotene recipients vs nonrecipients. Regarding duration of intervention effects and potential late effects, the excess risk for β-carotene recipients was no longer evident 4 to 6 years after ending the intervention and was primarily due to cardiovascular diseases.

Conclusions The beneficial and adverse effects of supplemental α-tocopherol and β-carotene disappeared during postintervention follow-up. The preventive effects of α-tocopherol on prostate cancer require confirmation in other trials. Smokers should avoid β-carotene supplementation.

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EPIDEMIOLOGICAL STUDIES SUGgest that low intake or having a low serum concentration of antioxidants is associated with elevated risk of cancer.[1,2] In the 1980s, 4 large randomized trials were initiated to assess whether antioxidants prevent cancer, cardiovascular disease, or both. In the Nutrition Intervention Trial I conducted in China among 29584 men and women aged 40 to 69 years, there was a 21% (95% confidence interval [CI], 1%-36%) reduction in stomach cancer mortality and a 13% (95% CI, 0%-25%) reduction in total cancer mortality in response to 5 years of supplementation with a combination of vitamin E, β-carotene, and selenium.[3]

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study assessed the effect of supplemental (1) α-tocopherol only, (2) β-carotene only, (3) α-tocopherol plus β-carotene, or (4) placebo on the incidence of lung cancer and other cancers among 29133 male smokers aged 50 to 69 years.[4] After a median of 6.1 years of follow-up, there was a 17% (95% CI, 2%-33%) higher incidence of lung cancer and 8% (95% CI, 1%-15%) higher total mortality among participants who received β-carotene compared with nonrecipients.[5,6] Supplementation with α-tocopherol had no effect on lung cancer incidence but did reduce the incidence of prostate cancer by 34% (95%

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CI, 14%-48%).[7] Of note, the original values for lung and prostate cancer during the trial period differ slightly from those presented herein because since the original reports were published,[6-7] 2 cases of lung cancer (1 individual diagnosed during the intervention period in the α-tocopherol-only group and 1 in the placebo group) and 2 cases of prostate cancer diagnosed during the intervention period (both individuals received β-carotene only) have been reported. Cases of carcinoid tumor previously reported were excluded from the present analysis (see below). The values herein represent current up-to-date data.

The Beta-Carotene and Retinol Efficacy Trial (CARET) assessed the combination of β-carotene and retinyl palmitate compared with placebo in 18 314 men and women aged 45 to 74 years, who were at high risk for lung cancer because of cigarette smoking and/or occupational asbestos exposure.[8] The results were similar to the ATBC Study: 28% (95% CI, 4%-57%) higher lung cancer incidence and 17% (95% CI, 3%-33%) higher total mortality in the group that received combination supplementation compared with those who received placebo after an average of 4 years.

In contrast, the Physicians' Health Study did not demonstrate an effect of β-carotene supplementation on lung cancer or overall mortality among 22 071 men aged 40 to 84 years after an average follow-up of 12 years.[9] However, only 11% of the Physicians' Health Study participants were current smokers, thus, the study population was at substantially lower risk for lung cancer compared with the participants in ATBC and CARET. Similarly, in a smaller controlled trial, the Skin Cancer Prevention Study, which involved 1805 men and women younger than 85 years, β-carotene supplementation had no effect on overall mortality.[10]

The intervention phase of the ATBC Study ended in April 1993. Because of the unexpected finding of increased lung cancer incidence from the trial, we were interested in observing patterns of disease in the postintervention period to determine the duration of the intervention effects and to observe potential late effects from the intervention. The study cohort has been monitored through the use of national registry data on mortality and cancer incidence. We report herein the posttrial findings for these events, reflecting 8 years of follow-up for total mortality and 6 years of follow-up for cancer incidence and cause-specific mortality. Findings from the intervention period for site-specific cancer incidence and for total mortality, the details of which have been previously reported,[5-7,11-14] are also presented herein to facilitate interpretation of the temporal relationships.

METHODS

The design of the ATBC Study has been described in detail elsewhere.[4] Briefly, this randomized, double-blind, placebo-controlled chemoprevention trial was conducted in Finland between 1985 and 1993, with the primary objective of evaluating the effect of α-tocopherol and β-carotene supplementation on the incidence of lung cancer and other cancers in 29 133 male smokers aged 50 to 69 years. The cohort was screened from a source population (n = 290 406) living in 14 adjoining areas in southwestern Finland. Recruitment began in April 1985 and continued through June 1988.

Individuals who were eligible and willing to participate in the trial were randomly allocated to 1 of the 4 treatment regimens: α-tocopherol only, β-carotene only, α-tocopherol plus β-carotene, or placebo. The formulation of the study agents was synthetic *dl*-α-tocopheryl acetate (50% powder) and synthetic β-carotene (10% water-soluble beadlets). The daily doses were 50 mg of α-tocopherol and 20 mg of β-carotene. Randomization was performed in blocks of 8 in each of the 14 study areas. The ATBC Study received approval from the institutional review board (IRB) of the National Public Health Institute of Finland and from the IRB of the National Cancer Institute (NCI). All participants provided written informed consent prior to randomization.

The trial continued until April 30, 1993, with the trial cohort followed up for cancer incidence and total mortality through national registries thereafter. At the end of the intervention phase, participants were informed by individual letter that the trial results and the available other knowledge did not indicate that α-tocopherol and β-carotene should be used for cancer prevention. Diet and use of supplements were not monitored during the postintervention follow-up because there was no active clinic-based follow-up. However, dietary assessment had been performed for all participants at baseline and repeated for approximately 800 randomly selected men annually to follow-up possible dietary changes during the intervention. No dietary changes were observed. Inquiry was made regarding use of nontrial supplements at every follow-up visit (which occurred 3 times annually during the intervention phase). Nurses instructed participants to discontinue use of high-dose vitamin E or β-carotene supplements.

We report herein the follow-up of those 25 563 participants still alive April 30, 1993, regarding incident cancers and cause-specific deaths through April 30, 1999 (6-year posttrial follow-up), and overall mortality through April 30, 2001 (8-year follow-up). The follow-up times are different because information on death is promptly available but official information on cause of death and identification and review of cancer cases is delayed. Because of the time required for study review of diagnosis of cancer cases, we allowed 2 years shorter follow-up time for cancer incidence and cause-specific mortality data than for the total mortality data so as to have as final and complete data as possible for cancer and cause-specific mortality.

The study was approved by the IRBs of the National Public Health Institute of Finland and the US NCI. The Ministry of Social Affairs and Health of Finland authorized the ATBC Study to obtain data from national health registers and sources such as hospitals and laboratories, extending to the end of 2002.

The NCI's IRB approved the posttrial follow-up without stipulating additional informed consent because participants would not be contacted or given invitations for further visits. Per NCI IRB requirements, the ATBC Study must report posttrial results to the IRB of the National Public Health Institute at regular intervals; the post-trial follow-up was evaluated by this board most recently in March 2003.

Assessment of End Points

Ascertainment of cancer cases during the intervention phase has been described.[4] During the posttrial follow-up, most cancer cases were identified via the Finnish Cancer Registry which provides almost 100% case coverage.[15] Some cancer cases were identified also through death certificates and the National Hospital Discharge Register. About 0.8% of cases were identified through death certificates and the National Hospital Discharge Register and were unknown to the Finnish Cancer Registry at the time of our most recent ascertainment of cases reported for the analysis herein.

The medical records of all potential cancer cases were collected from the hospitals and pathology laboratories. Two oncologists independently reviewed the records of all reported prostate, stomach, colorectal, and pancreatic cancers as well as cancers recorded as having an unknown primary site. In the case of disagreement between 2 oncologists, a third oncologist reviewed the documents and assigned the final diagnosis. Disagreement on cancer diagnosis was uncommon (eg, of 672 postintervention prostate cancer cases, the oncologists disagreed on only 1 case [0.15%]). In addition, a pathologist reviewed the histopathologic and cytological specimens from these cases.

One study physician reviewed centrally the medical records of cases of other cancer sites to confirm the cancer diagnoses. During review of the cancer cases that arose during the intervention period, it became evident that the cancer diagnosis was seldom different between the 2 reviewers. Thus, for posttrial review, the decision was made to have 2 oncologists independently review only cases with unknown primary sites reported by the Finnish Cancer Registry and sites for which there was interest in more detailed data (eg, stage for prostate cancer).

In this report, we include results for cancers of lung, prostate, urinary tract (renal pelvis, ureter, and bladder), colon and rectum (excluding cancers of anal canal), stomach, pancreas (excluding endocrine tumors), and kidney. Other cancers (excluding nonmelanoma skin cancer) are combined.

In situ carcinomas were included among the urinary tract cancers (8 posttrial cases) but not for other organ sites (14 cases). Carcinoid tumors are excluded because of the difficulty in ascertaining their malignancy (16 posttrial cases). The 16 postintervention cases were distributed into trial groups as follows: 6 cases were in the α-tocopherol-only group, 4 in the β-carotene-only group, 3 in the group receiving α-tocopherol plus β-carotene, and 3 in the placebo group. A lung carcinoid tumor from the intervention period in the α-tocopherol plus β-carotene group was excluded from the analysis herein but was included in a prior report.[6] A previously reported stomach carcinoid tumor in the α-tocopherol-only group from the intervention period was also excluded.[14]

Deaths were identified from the Register of Causes of Death. Specific causes were derived from the official underlying cause of death.

The present numbers of lung, prostate, and stomach cancer cases during intervention differ slightly from those reported earlier[6,7,14] because we excluded carcinoid tumors and identified some new cases diagnosed during the intervention period. Since the original reports,[6,7] 2 cases of lung cancer (1 individual diagnosed during the intervention period in the α-tocopherol-only group and 1 in the placebo group) and 2 cases of prostate cancer (both diagnosed during the intervention period and had received β-carotene only) have been reported. Prior publications[6,14] included 1 case of a stomach carcinoid tumor from the intervention period in the α-tocopherol-only group and a lung carcinoid tumor from the intervention period in the α-tocopherol plus β-carotene group. Both cases were excluded from the present analysis.

Statistical Analysis

In the analysis of cancer incidence, follow-up continued from the date of randomization until the first occurrence of a specific cancer, death, or the administratively defined end of follow-up (ie, April 30, 1999). In the analyses of cause-specific and total mortality, follow-up continued until death or the end of follow-up (April 30, 1999, for cause-specific mortality and April 30, 2001, for total mortality). In all analyses, censoring was assumed to be independent of the end point. Some participants had more than 1 type of tumor. All cases were reviewed centrally by 1 or 2 ATBC Study physicians who confirmed that the individual had more than 1 malignancy. A participant was counted only once in the cancer-specific analyses (ie, only the first occurrence of an organ-specific cancer was included), but if he had 2 different organ-specific cancers, he was included in both analyses (eg, in the analyses of both lung and prostate cancer).

We divided the follow-up period into 4 intervals to demonstrate temporal changes in the effects of α-tocopherol and β-carotene: (1) trial period (April 1985-April 30, 1993); (2) posttrial period 1 (May 1, 1993-April 30, 1996); (3) posttrial period 2 (May 1, 1996-April 30, 1999); and (4) posttrial period 3 for the analysis of total mortality only (May 1, 1999-April 30, 2001). Within these periods, crude rates per 10 000 person-years were calculated in each of the 4 groups and according to the 2×2 factorial design. Crude relative risk (RR) point estimates and their 95% CIs for these periods were obtained using a Poisson regression model.[16] Statistical analyses were performed using S-PLUS version 3.4 for Unix (MathSoft Inc, Seattle, Wash).

To estimate the calendar time-specific RRs for lung cancer incidence and total mortality, we calculated smoothed RR estimates and their 95% pointwise CIs using a generalized additive model.[17] We first divided calendar time into monthly intervals with the exception that we combined calendar time until April 1986 for the first interval because the risk sets were small at this earliest phase of the recruitment period that started in 1985. The monthly rates were treated as Poisson responses. For each target time point, 40% of all monthly observations nearest to the target were used to define a neighborhood for which a weighted linear curve was used to estimate the RR at the target point. The weights for the monthly observations around the target point were calculated from a tricube kernel centered at the target point. The 40% neighborhood was chosen after the examination of smoothed curves with different values because fluctuation of RRs for the lower values made the overall interpretation difficult and a great deal of detail was lost for the higher values.

Cause-specific data on deaths are presented in mutually exclusive cause-of-death categories based on the following *International Classification of Diseases, Eighth Revision (ICD-8)*, *International Classification of Diseases, Ninth Revision (ICD-9)*, and *International Classification of Diseases, 10th Revision (ICD-10)* codes: lung cancer (*ICD-8* and *ICD-9* 162; *ICD-10* C33-C34); other cancer (*ICD-8* 140-161 and 163-207; *ICD-9* 140-161 and 163-208; *ICD-10* C00-C32 and C37-C97); ischemic heart disease (*ICD-8* and *ICD-9* 410-414; *ICD-10* I20-I25); hemorrhagic stroke (*ICD-8* 430-431; *ICD-9* 430-432; *ICD-10* I60-I62); nonhemorrhagic cerebrovascular disease (*ICD-8* 432-438; *ICD-9* 433-438; *ICD-10* I63-I69); other cardiovascular disease (*ICD-8* 390-404, 420-429, and 440-458; *ICD-9* 390-405, 415-429, and 440-459; *ICD-10* I00-I15, I26-I52, and I70-I99); respiratory disease (*ICD-8* and *ICD-9* 460-519; *ICD-10* J00-J99); and other causes (*ICD-8* 000-139, 208-389, and 520-999; *ICD-9* 001-139, 210-389, and 520-999; *ICD-10* A00-B99, D00-H95, and K00-Y98).

RESULTS

Participant Characteristics

Of the original randomized ATBC Study cohort, 25563 men were still

Table 1. Incidence and Relative Risk of Site-Specific Cancer During the Trial by Regimen*

Site of Cancer	Trial (April 1985-April 1993)			
	Placebo	α-Tocopherol	α-Tocopherol Plus β-Carotene	β-Carotene
Lung				
No. at risk	7287	7286	7278	7282
No. of incident cancers	209	205	239	242
Rate per 10 000 person-years	49.3	48.5	56.8	57.4
RR (95% CI)†	Referent	0.98 (0.81-1.19)	1.15 (0.96-1.38)	1.16 (0.97-1.40)
Prostate				
No. at risk	7287	7286	7278	7282
No. of incident cancers	67	43	56	82
Rate per 10 000 person-years	15.8	10.2	13.3	19.4
RR (95% CI)†	Referent	0.64 (0.44-0.94)	0.84 (0.59-1.20)	1.23 (0.89-1.70)
Urothelial‡				
No. at risk	7287	7286	7278	7282
No. of incident cancers	37	47	42	43
Rate per 10 000 person-years	8.7	11.1	9.9	10.2
RR (95% CI)†	Referent	1.27 (0.83-1.96)	1.14 (0.73-1.78)	1.17 (0.75-1.81)
Stomach				
No. at risk	7287	7286	7278	7282
No. of incident cancers	24	31	37	33
Rate per 10 000 person-years	5.6	7.3	8.7	7.8
RR (95% CI)†	Referent	1.29 (0.76-2.21)	1.55 (0.93-2.59)	1.38 (0.82-2.34)
Kidney§				
No. at risk	7287	7286	7278	7282
No. of incident cancers	27	27	27	21
Rate per 10 000 person-years	6.4	6.4	6.4	5.0
RR (95% CI)†	Referent	1.00 (0.59-1.71)	1.01 (0.59-1.71)	0.78 (0.44-1.38)
Pancreas				
No. at risk	7287	7286	7278	7282
No. of incident cancers	26	25	26	12
Rate per 10 000 person-years	6.1	5.9	6.1	2.8
RR (95% CI)†	Referent	0.96 (0.56-1.67)	1.01 (0.58-1.73)	0.46 (0.23-0.92)
Colorectal				
No. at risk	7287	7286	7278	7282
No. of incident cancers	37	29	30	39
Rate per 10 000 person-years	8.7	6.8	7.1	9.2
RR (95% CI)†	Referent	0.78 (0.48-1.28)	0.81 (0.50-1.32)	1.06 (0.67-1.66)
Other				
No. at risk	7287	7286	7278	7282
No. of incident cancers	124	131	122	130
Rate per 10 000 person-years	29.3	31.0	28.9	30.8
RR (95% CI)†	Referent	1.06 (0.83-1.36)	0.99 (0.77-1.27)	1.05 (0.82-1.34)

Abbreviations: CI, confidence interval; RR, relative risk.
*Of note, the original values for lung and prostate cancer during the trial period differ slightly from those presented herein because since the original reports,[6-7] 2 cases of lung cancer (1 individual diagnosed in the intervention period in the α-tocopherol-only group and 1 in the placebo group) and 2 cases of prostate cancer (both diagnosed during the intervention period and had received β-carotene only) have been reported. Cases of carcinoid tumor previously reported were excluded from the present analysis (see text). The values herein represent current, up-to-date data. Trial period values for urothelial, stomach, kidney, pancreas, and colorectal tumors also have been previously published.[11-14]
†RR estimate from a Poisson regression model and 95% CI is approximate.
‡Includes cancers of renal pelvis, ureter, and bladder.
§Includes renal cell carcinoma.

alive at the beginning of the posttrial follow-up in May 1993. At that time, their average age was 63.5 years, and similar across the 4 supplementation groups (range of means, 63.4-63.6 years). At the beginning of the trial in 1985-1988, they reported smoking an average of 20.4 cigarettes daily and having smoked for 35.5 years. Of the individuals in posttrial follow-up, 79% had their last trial follow-up visit in the winter of 1992-1993. At this visit, 75% were still current smokers (range, 74.6%-75.4% across the 4 study groups) who smoked a mean of 18.1 cigarettes daily (range, 17.9-18.2 cigarettes). Similarly, 4.8% reported taking nontrial supplements containing vitamin E and 0.6% reported taking supplements containing β-carotene. The average daily dose from supplement intake was 20 mg for vitamin E and 7 mg for β-carotene.

Cancer Incidence

Incidences and RRs of site-specific cancers in the 4 study groups for the trial period are shown in TABLE 1 and for the

Table 2. Incidence and Relative Risk of Site-Specific Cancer During Posttrial Follow-up by Regimen

	Posttrial Period							
	May 1993-April 1996				May 1996-April 1999			
Site of Cancer	Placebo	α-Tocopherol	α-Tocopherol Plus β-Carotene	β-Carotene	Placebo	α-Tocopherol	α-Tocopherol Plus β-Carotene	β-Carotene
Lung								
No. at risk	6375	6349	6278	6281	5782	5780	5651	5625
No. of incident cancers	120	112	126	140	130	147	140	122
Rate per 10 000 person-years	65.6	61.5	70.3	78.1	79.4	90.5	88.2	77.3
RR (95% CI)*	Referent	0.94 (0.73-1.21)	1.07 (0.83-1.38)	1.19 (0.93-1.52)	Referent	1.14 (0.90-1.44)	1.11 (0.87-1.41)	0.97 (0.76-1.25)
Prostate								
No. at risk	6388	6388	6308	6306	5745	5788	5622	5615
No. of incident cancers	74	54	76	73	104	98	87	106
Rate per 10 000 person-years	40.5	29.6	42.4	40.7	64.2	60.6	55.3	67.6
RR (95% CI)*	Referent	0.73 (0.51-1.04)	1.05 (0.76-1.44)	1.00 (0.73-1.39)	Referent	0.94 (0.72-1.24)	0.86 (0.65-1.15)	1.05 (0.80-1.38)
Urothelial†								
No. at risk	6408	6386	6315	6328	5793	5801	5668	5662
No. of incident cancers	27	30	26	25	30	29	37	30
Rate per 10 000 person-years	14.7	16.4	14.5	13.9	18.3	17.8	23.3	18.9
RR (95% CI)*	Referent	1.12 (0.66-1.88)	0.98 (0.57-1.68)	0.94 (0.55-1.62)	Referent	0.97 (0.58-1.62)	1.27 (0.79-2.06)	1.03 (0.62-1.71)
Stomach								
No. at risk	6421	6408	6331	6345	5821	5836	5699	5691
No. of incident cancers	15	16	22	19	11	18	11	12
Rate per 10 000 person-years	8.1	8.7	12.2	10.5	6.7	11.0	6.9	7.5
RR (95% CI)*	Referent	1.07 (0.53-2.16)	1.50 (0.78-2.88)	1.29 (0.65-2.53)	Referent	1.65 (0.78-3.49)	1.03 (0.45-2.38)	1.13 (0.50-2.55)
Kidney‡								
No. at risk	6427	6406	6333	6351	5820	5836	5704	5691
No. of incident cancers	16	12	13	13	14	14	14	12
Rate per 10 000 person-years	8.7	6.5	7.2	7.2	8.5	8.5	8.7	7.5
RR (95% CI)*	Referent	0.75 (0.36-1.59)	0.83 (0.40-1.72)	0.83 (0.40-1.72)	Referent	1.01 (0.48-2.11)	1.03 (0.49-2.16)	0.88 (0.41-1.91)
Pancreas								
No. at risk	6435	6416	6346	6360	5837	5847	5718	5710
No. of incident cancers	15	16	14	16	18	16	15	17
Rate per 10 000 person-years	8.1	8.7	7.7	8.8	10.9	9.7	9.3	10.6
RR (95% CI)*	Referent	1.07 (0.53-2.17)	0.95 (0.46-1.97)	1.08 (0.54-2.19)	Referent	0.89 (0.46-1.75)	0.86 (0.43-1.70)	0.97 (0.50-1.89)
Colorectal								
No. at risk	6416	6403	6330	6340	5806	5825	5696	5677
No. of incident cancers	20	25	25	22	18	22	35	38
Rate per 10 000 person-years	10.9	13.6	13.9	12.2	10.9	13.4	21.9	23.9
RR (95% CI)*	Referent	1.25 (0.70-2.26)	1.27 (0.71-2.29)	1.12 (0.61-2.05)	Referent	1.23 (0.66-2.29)	2.00 (1.13-3.54)	2.18 (1.25-3.82)
Other								
No. at risk	6376	6360	6297	6312	5752	5781	5647	5636
No. of incident cancers	79	74	74	71	85	75	81	74
Rate per 10 000 person-years	43.3	40.7	41.3	39.5	52.2	46.2	51.1	46.8
RR (95% CI)*	Referent	0.94 (0.68-1.29)	0.95 (0.69-1.31)	0.91 (0.66-1.26)	Referent	0.89 (0.65-1.21)	0.98 (0.72-1.33)	0.90 (0.66-1.22)

Abbreviations: CI, confidence interval; RR, relative risk.
*RR estimate from a Poisson regression model and 95% CI is approximate.
†Includes cancers of renal pelvis, ureter, and bladder.
‡Includes renal cell carcinoma.

posttrial periods 1 and 2 are shown in TABLE 2. TABLE 3 presents the respective RRs according to supplementation with α-tocopherol and β-carotene.

During the 6-year posttrial period, 1037 incident lung cancer cases were ascertained among the 25 283 participants who had no lung cancer diagnosed when the posttrial period began. No significant overall difference in lung cancer incidence was observed during the posttrial period between α-tocopherol recipients and nonrecipients (RR, 1.03; 95% CI, 0.91-1.16) or between β-carotene recipients and nonrecipients (RR, 1.06; 95% CI, 0.94-1.20). Although not statistically significant, α-tocopherol appeared to reduce lung cancer risk slightly during the first 3 posttrial years, whereas it appeared to increase the risk somewhat during the later years (Table 3). The elevated risk of lung cancer in the β-carotene group observed during the trial continued during the first posttrial period, although statistically nonsignificant (Table 3). The smoothed calendar time-specific RRs for the α-tocopherol recipients compared with nonrecipients were below 1.0 for the last years of the intervention period and the first posttrial years, but increased somewhat with longer follow-up (FIGURE 1A). For the β-carotene recipients compared with nonrecipients, the RRs increased during the intervention but declined thereafter, falling below 1.0 approximately 4 years posttrial (Figure 1B).

There were 672 incident prostate cancer cases during the 6-year posttrial follow-up among the 25 390 participants who had no prostate cancer diagnosed by May 1, 1993. No statistically significant difference in prostate cancer incidence was observed between α-tocopherol recipients and nonrecipients, although reduced risk was suggested (RR, 0.88; 95% CI, 0.76-1.03). β-carotene showed no effect postintervention (RR, 1.06; 95% CI, 0.91-1.23).

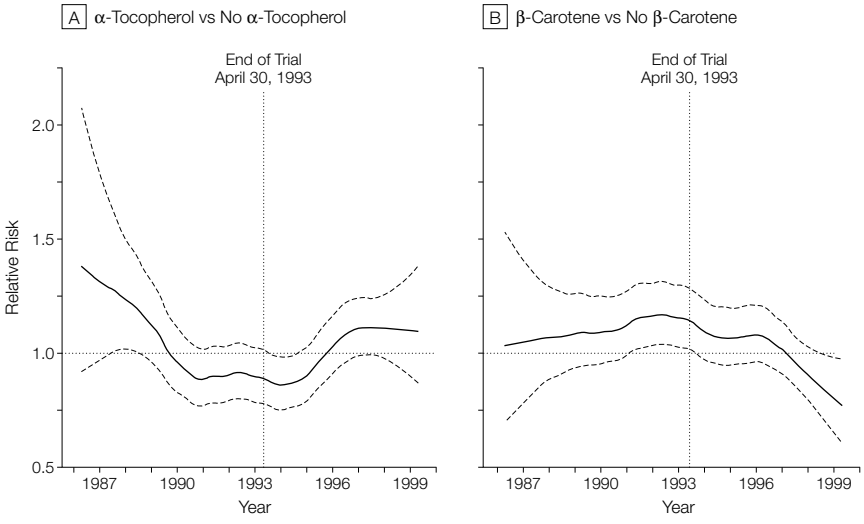
The incidences of other cancers were low compared with those of lung cancer and prostate cancer, and thus their RR estimates were relatively imprecise (Table 1, Table 2, and Table 3). The risk of colorectal cancer during the follow-up was elevated for β-carotene recipients compared with nonrecipients (RR, 1.44; 95% CI, 1.09-1.90), but the elevation occurred only during the second posttrial period (Table 3).

Table 3. Relative Risk of Site-Specific Cancer by α-Tocopherol or β-Carotene Supplementation*

Site of Cancer	Trial (April 1985-April 1993)	Posttrial Period	
		May 1993-April 1996	May 1996-April 1999
α-Tocopherol vs No α-Tocopherol			
Lung	0.99 (0.87-1.12)	0.92 (0.77-1.09)	1.14 (0.96-1.35)
Prostate	0.66 (0.52-0.86)	0.89 (0.70-1.12)	0.88 (0.72-1.07)
Urothelial†	1.11 (0.82-1.51)	1.08 (0.74-1.58)	1.10 (0.78-1.57)
Stomach	1.19 (0.84-1.70)	1.12 (0.71-1.78)	1.26 (0.73-2.19)
Kidney‡	1.13 (0.76-1.66)	0.87 (0.51-1.48)	1.08 (0.63-1.84)
Pancreas	1.34 (0.88-2.05)	0.97 (0.59-1.60)	0.89 (0.55-1.44)
Colorectal	0.78 (0.55-1.09)	1.19 (0.79-1.80)	1.02 (0.70-1.47)
Other	1.00 (0.84-1.19)	0.99 (0.79-1.24)	0.98 (0.79-1.23)
β-Carotene vs No β-Carotene			
Lung	1.17 (1.02-1.33)	1.17 (0.98-1.39)	0.97 (0.82-1.15)
Prostate	1.26 (0.98-1.62)	1.18 (0.94-1.50)	0.98 (0.81-1.20)
Urothelial†	1.02 (0.75-1.37)	0.91 (0.62-1.33)	1.17 (0.82-1.66)
Stomach	1.28 (0.90-1.82)	1.34 (0.84-2.14)	0.81 (0.47-1.41)
Kidney‡	0.89 (0.60-1.32)	0.94 (0.55-1.61)	0.95 (0.56-1.63)
Pancreas	0.75 (0.49-1.14)	0.98 (0.59-1.62)	0.97 (0.60-1.57)
Colorectal	1.05 (0.75-1.47)	1.06 (0.70-1.60)	1.88 (1.28-2.76)
Other	0.99 (0.83-1.18)	0.96 (0.77-1.21)	0.99 (0.80-1.24)

*Values are expressed as relative risk (95% confidence interval). RR estimate from a Poisson regression model and 95% CI is approximate. Of note, the original values for lung and prostate cancer during the trial period differ slightly from those presented herein because since the original reports,[6-7] 2 cases of lung cancer (1 individual diagnosed in the intervention period in the α-tocopherol-only group and 1 in the placebo group) and 2 cases of prostate cancer (both diagnosed during the intervention period and had received β-carotene only) have been reported. Cases of carcinoid tumor previously reported were excluded from the present analysis (see text). The values herein represent current, up-to-date data. Trial period values for urothelial, stomach, kidney, pancreas, and colorectal tumors also have been previously published.[11-14]
†Includes cancers of renal pelvis, ureter, and bladder.
‡Includes renal cell carcinoma.

Figure 1. Lung Cancer Incidence for Participants in the ATBC Study



Smoothed relative risk curves and their 95% pointwise confidence intervals in calendar time. ATBC indicates Alpha-Tocopherol, Beta-Carotene Cancer Prevention.

Mortality

Of the 25 563 participants still alive at the beginning of the posttrial follow-up (May 1, 1993), 7261 (28%) died by April 30, 2001. TABLE 4 shows the rates and RRs of mortality in the 4 regimen groups both for the trial period and for the 8-year posttrial follow-up, divided into 3 periods (ie, 3+3+2 years). TABLE 5 presents the respective RRs according to supplementation with α-tocopherol and β-carotene. During the 8-year posttrial follow-up, the relative mortality was 1.01 (95% CI, 0.96-1.05) among α-tocopherol recipients compared with nonrecipients and 1.07 (95% CI, 1.02-1.12) among β-carotene recipients compared with nonrecipients.

The smoothed calendar time-specific relative mortality rate of α-tocopherol recipients was similar to that of nonrecipients throughout the postintervention period (FIGURE 2A). The higher mortality rate of the β-carotene recipients compared with that of nonrecipients evident by the end of intervention returned toward the null approximately 4 to 6 years later (Figure 2B).

A total of 5298 deaths were identified during the 6-year posttrial follow-up from May 1993 to April 1999. Of these, 28.8% (n=1524) were attributed to ischemic heart disease, 17.8% (n=942) to lung cancer, 17.1% (n=905) to other cancers, 8.2% (n=433) to respiratory disease, 4.9% (n=261) to nonhemorrhagic cerebrovascular disease, 2.6% (n=139) to hemorrhagic stroke, 7.0% (n=372) to other cardiovascular disease, and 13.6% (n=722) to other causes. FIGURE 3 presents RR estimates by cause of death in the 2 group comparisons separately for the trial period and for the 6-year posttrial follow-up. The excess mortality due to hemorrhagic stroke observed for α-tocopherol recipients during the trial was also present during the posttrial period (81 vs 58 deaths; RR, 1.40; 95% CI, 1.00-1.96). However, of the 23 excess cases of fatal hemorrhagic stroke, 19 cases (83%) appeared in the α-tocopherol plus β-carotene group and only 4 cases (17%) in the α-tocopherol-only group. In addition, half of the excess cases occurred only during the sixth posttrial year. Most of the excess deaths in the β-carotene group were from cardiovascular disease.

Table 4. Rate and Relative Risk of Mortality by Regimen

	Placebo	α-Tocopherol	α-Tocopherol Plus β-Carotene	β-Carotene
Trial (April 1985-April 1993)				
No. at risk	7287	7286	7278	7282
No. of deaths	851	868	932	919
Rate per 10 000 person-years	200	204	220	217
RR (95% CI)*	Referent	1.02 (0.93-1.12)	1.10 (1.00-1.21)	1.08 (0.99-1.19)
Posttrial (May 1993-April 1996)				
No. at risk	6436	6418	6346	6363
No. of deaths	598	566	627	651
Rate per 10 000 person-years	324	308	346	358
RR (95% CI)*	Referent	0.95 (0.85-1.07)	1.07 (0.96-1.20)	1.11 (0.99-1.24)
Posttrial (May 1996-April 1999)				
No. at risk	5838	5852	5719	5712
No. of deaths	668	733	727	728
Rate per 10 000 person-years	403	445	452	453
RR (95% CI)*	Referent	1.10 (0.99-1.23)	1.12 (1.01-1.25)	1.12 (1.01-1.25)
Posttrial (May 1999-April 2001)				
No. at risk	5170	5119	4992	4984
No. of deaths	488	504	476	495
Rate per 10 000 person-years	493	519	500	521
RR (95% CI)*	Referent	1.05 (0.93-1.19)	1.01 (0.89-1.15)	1.06 (0.93-1.20)

Abbreviations: CI, confidence interval; RR, relative risk.
*RR estimate from a Poisson regression model and 95% CI is approximate.

Table 5. Relative Risk of Mortality by α-Tocopherol or β-Carotene Supplementation

	RR (95% CI)*	
Study Period	α-Tocopherol vs No α-Tocopherol	β-Carotene vs No β-Carotene
April 1985-April 1993	1.02 (0.95-1.09)	1.08 (1.01-1.15)
May 1993-April 1996	0.96 (0.89-1.04)	1.11 (1.03-1.21)
May 1996-April 1999	1.05 (0.97-1.13)	1.07 (0.99-1.15)
May 1999-April 2001	1.00 (0.92-1.10)	1.01 (0.92-1.10)

Abbreviations: CI, confidence interval; RR, relative risk.
*RR estimate from a Poisson regression model and 95% CI is approximate.

COMMENT

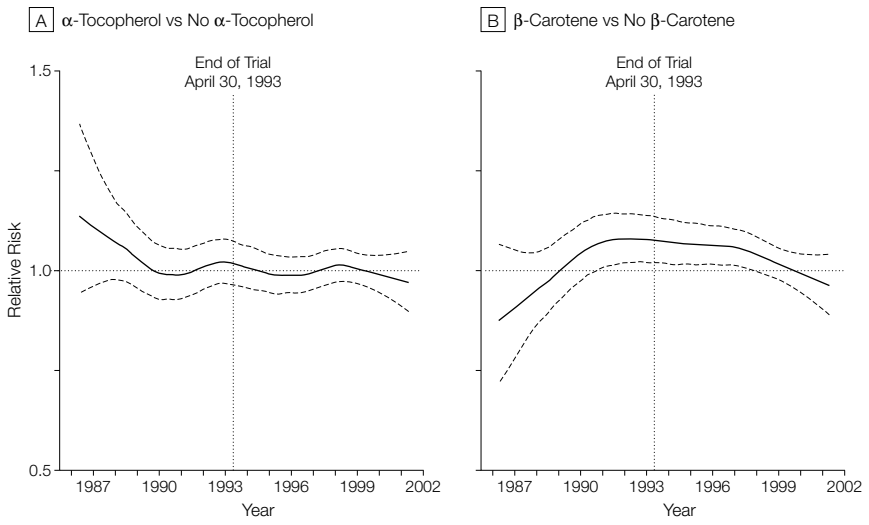
The primary aim of the ATBC Study was to determine whether supplementation with α-tocopherol or β-carotene would reduce the incidence of lung cancer in male smokers. At the conclusion of the 6 year (median) intervention, we observed no overall effect of α-tocopherol on lung cancer incidence, whereas β-carotene increased the rate by 17%.[6] This increased risk appeared approximately 4 years after starting β-carotene supplementation and is shown in the present analysis to disappear within a similar timeframe postintervention. The CARET study used a combination of β-carotene and vitamin A in smokers and asbestos-exposed workers and showed a time lag of about 18 months to increased lung cancer incidence during its supplementation period.[8] These temporal effects suggest that β-carotene in some way accelerated the progression and led to earlier clinical diagnosis of more advanced latent lung tumors. Those effects also argue against a promotional effect of β-carotene on earlier phases of lung carcinogenesis. Whether the lower rates of lung cancer we observed after 4 years of stopping β-carotene supplementa-

tion merely reflect fewer lung cancer diagnoses within the now diminished pool of at-risk subclinical cases, or the possibility that β-carotene may exert long-term preventive effects on earlier phases of lung carcinogenesis, may become evident during extended follow-up of this and other trial cohorts.

The mechanisms by which β-carotene affects the development of lung cancer have not yet been determined. Experimental data, however, suggest that β-carotene does not induce genotoxic effects per se.[18] The most widely suggested hypothesis is that components of cigarette smoke in the presence of the relatively high oxygen tension in the lung combine to induce oxidation of β-carotene, resulting in a prooxidant effect.[19] However, a study involving human bronchial epithelial cells found no direct prooxidant effect of the smoke-induced β-carotene oxidation products.[20]

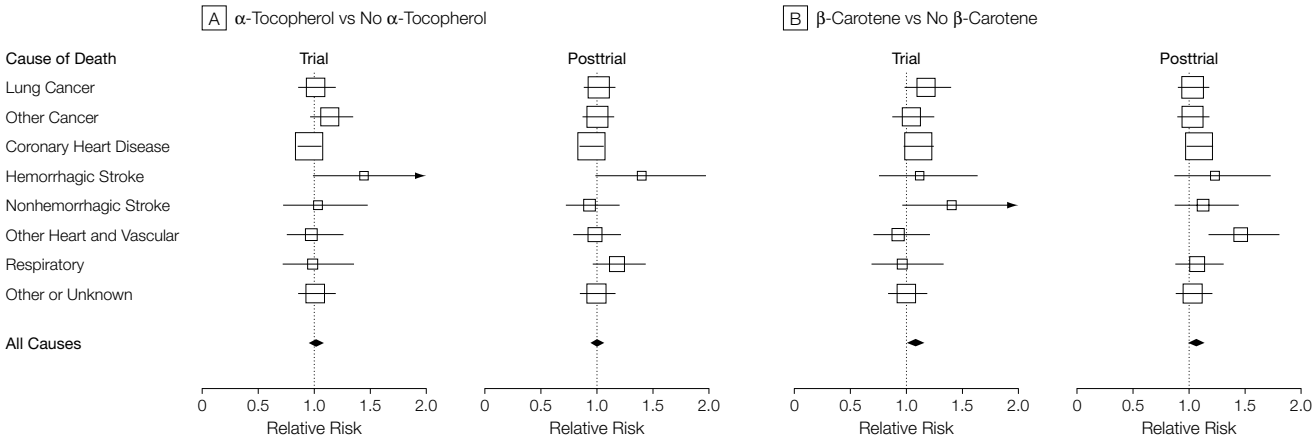
Other mechanisms by which β-carotene–smoke interactions could increase lung carcinogenesis have been recently reported. Ferrets given β-carotene supplements (equivalent to 30 mg/day in humans) and exposed to cigarette smoke had a strong proliferative response in their lung tissue in addition to diminished retinoid signaling resulting from suppression of retinoic acid receptor β gene expression and overexpression of activator protein 1.[21] The effect appeared dose-dependent because a physiological dose compared with low intake of β-carotene (equivalent to 6 mg/day and 2.1 mg/day) had no potentially detrimental effects and afforded weak protection against smoke-induced lung damage.[22] Paolini et al[23,24] reported that β-carotene in the rat lung produced a powerful booster effect on several carcinogen-metabolizing P450 enzymes, and that this was associated with the generation of oxidative stress. These effects may predispose to cancer through bioactivation of tobacco smoke procarcinogens and oxidation of β-carotene to a prooxidant.[23,24] However, these experiments require cautious interpretation because they are based on exposure of nonmalignant bronchial epi-

Figure 2. Total Mortality for Participants in the ATBC Study



Smoothed relative risk curves and their 95% pointwise confidence intervals in calendar time. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention.

Figure 3. Cause-Specific Mortality for Participants in the ATBC Study



Relative risk estimates for comparisons during the trial and during the 6-year posttrial follow-up. The whiskers span the 95% confidence intervals. The size of the squares is proportional to the proportion of all deaths (diamonds) due to each cause-specific group. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention.

thelial cell lines or lung tissue, whereas the findings from the ATBC Study and CARET suggest that β-carotene advances the progression of lung cancer in a chronically high-risk organ with abnormal cells and/or latent tumors already present.

The α-tocopherol supplementation in the ATBC Study reduced the incidence of prostate cancer by 34%, with the preventive effect observed approximately 18 months after the start of intervention.[7] This effect was present throughout the 6-year posttrial follow-up evaluated herein, but was substantially attenuated even within the first 3 posttrial years. This suggests that α-tocopherol prevents the progression of prostate cancer in a later phase of carcinogenesis, and that this effect is transient, diminishing fairly rapidly following cessation of supplementation.

Although laboratory experiments point to several potential mechanisms for a cancer preventive effect of α-tocopherol,[25] observational studies have provided only weak support for the vitamin E prostate cancer hypothesis thus far.[26] In the Heart Protection Study, a randomized placebo-controlled trial involving more than 15 000 men aged 40 to 80 years, a 9% nonsignificant decrease in risk of prostate cancer with a daily combination of vitamin E (600 mg), vitamin C (250 mg), and β-carotene (20 mg) for 5 years was observed.[27] The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was recently launched to assess the effects of up to 12 years of supplementation with selenium and vitamin E in the prevention of prostate cancer among 32 400 men in North America.[28] The modest but statistically nonsignificant increase in risk of prostate cancer among β-carotene recipients in the ATBC Study was reduced in the early posttrial period and absent in the later posttrial years. These observations, together with the finding of no effect of β-carotene in the CARET and Physicians' Health Study, collectively reflecting over 1300 prostate cancer cases, suggest that β-carotene does not affect the development of clinical prostate cancer.

Neither α-tocopherol nor β-carotene supplementation had significant overall effects on other major cancers during the postintervention period, with the exception of a late increase in colorectal cancer incidence in the β-carotene–supplemented group. Although this may be a chance finding, an effect on early colorectal carcinogenesis, including possible progression of adenomatous polyps, cannot be excluded. It is also possible that late posttrial differences may potentially be influenced by competing causes of death.

Total mortality during the intervention period was 8% higher among men who received β-carotene compared with those who did not, and excess mortality was also observed during the posttrial follow-up. The higher trial period mortality was due to coronary heart disease and lung cancer, whereas during the posttrial follow-up it was due primarily to cardiovascular causes, including coronary heart disease, cardiomyopathy, hypertensive heart disease, stroke, and aortic rupture. We do not know of a common mechanism that would explain how β-carotene might increase mortality across this diverse spectrum of cardiovascular diseases. Our assessment of the duration of increased mortality following β-carotene supplementation suggests that the excess mortality lasted for 4 to 6 years, roughly the equivalent time it took for the excess to become evident following the initiation of the intervention.

Supplementation with α-tocopherol increased hemorrhagic stroke mortality by 45% during the intervention. An elevated risk (40%) was observed also in the posttrial period. Half of this excess occurred in the sixth posttrial year, however, and the annual numbers of fatal hemorrhagic stroke cases were small, approximately 20. We do not know of a hypothesis that would explain such a late effect; thus, the posttrial finding is likely due to chance. The possibility that α-tocopherol inhibits platelet function, which is consistent with the increased risk of hemorrhagic stroke during the intervention period and its disappearance shortly after stopping α-tocopherol supplementation, however, cannot be excluded. On the other hand, in the Heart Protection Study daily supplementation with a combination of vitamin E, vitamin C, and β-carotene had no effect on the incidence of hemorrhagic stroke when compared with placebo (51 vs 53 cases, respectively) but no data on fatal hemorrhagic stroke were reported.[27]

In conclusion, large-scale controlled trials have not produced consistent evidence for the efficacy of α-tocopherol or β-carotene in the prevention of cancer. There is, however, consistent evidence that β-carotene supplementation in smokers increases the risk of lung cancer and total mortality. The cumulative experience of nearly 16 years and nearly 350 000 person-years of observation during the intervention and postintervention follow-up of participants in the ATBC Study suggests a symmetry in the effect of β-carotene on these events, with the disappearance of risk occurring within the time it became evident. Furthermore, the posttrial follow-up did not reveal any late preventive effects on cancer.

Thus, the recommendations made at the time our initial trial results were reported remain appropriate: the possible preventive effect of α-tocopherol on prostate cancer requires confirmation from other trials before public health recommendations can be made for vitamin E. Also, β-carotene supplementation should be avoided by smokers since it may be harmful to them.

Author Contributions: Dr Virtamo, as a principal investigator of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Follow-up, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Virtamo, Albanes, Pietinen, Huttunen, Taylor.
Acquisition of data: Malila, Virtamo.
Analysis and interpretation of data: Virtamo, Albanes, Korhonen, Malila, Virtanen, Albert, Taylor, Huttunen.
Drafting of the manuscript: Virtamo, Korhonen, Virtanen, Malila.
Critical revision of the manuscript for important intellectual content: Huttunen, Albanes, Taylor, Pietinen, Albert.

Statistical expertise: Korhonen, Virtanen, Albert. *Obtaining funding:* Virtamo, Pietinen, Albanes. *Administrative, technical, or material support:* Virtamo, Pietinen, Albanes. *Study supervision:* Virtamo, Albanes, Huttunen, Taylor.

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